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=> d 155 bib ab tech abex tot

L55 ANSWER 1 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 AN 2004-375904 [35] WPIX Full-text
 DNC C2004-141379 [35]
 TI Preparation of 3-hydroxy-5-beta-H-steroidal sapogenin
 derivatives used to treat cognitive dysfunction comprises reduction of
 3-keto-5-beta-H-steroidal sapogenin using agent comprising a
 hindered organoborane or an organo-aluminium
 hydride
 DC B01
 IN GUNNING P J; TIFFIN P D
 PA (PHYT-N) PHYTOPHARM PLC; (PHYT-N) PHYTOTECH LTD
 CYC 103
 PIA WO 2004037845 A1 20040506 (200435)* EN 41[0]
 AU 2003224308 A1 20040513 (200468) EN
 EP 1558627 A1 20050803 (200551) EN
 BR 2003015746 A 20050906 (200560) PT
 TW 2004006215 A 20040501 (200571) ZH
 US 20060041119 A1 20060223 (200615) EN <--
 JP 2006507360 W 20060302 (200621) JA 31
 CN 1723218 A 20060118 (200639) ZH
 IN 2005MN00308 P3 20060505 (200659) EN
 KR 2005090379 A 20050913 (200674) KO
 ADT WO 2004037845 A1 WO 2003-GB1780 20030428; AU 2003224308 A1 AU
 2003-224308 20030428; BR 2003015746 A BR 2003-15746 20030428; CN 1723218 A
 CN 2003-824744 20030428; EP 1558627 A1 EP 2003-720733 20030428; TW
 2004006215 A TW 2003-109883 20030428; EP 1558627 A1 WO 2003-GB1780
 20030428; BR 2003015746 A WO 2003-GB1780 20030428; US
 20060041119 A1 WO 2003-GB1780 20030428; JP 2006507360 W
 WO 2003-GB1780 20030428; IN 2005MN00308 P3 WO 2003-GB1780

20030428; JP 2006507360 W JP 2005-501542 20030428; IN 2005MN00308 P3
 IN 2005-MN308 20050420; US 20060041119 A1 US 2005-531086
 20050621; KR 2005090379 A WO 2003-GB1780 20030428; KR
 2005090379 A KR 2005-707429 20050428

FDT AU 2003224308 A1 Based on WO 2004037845 A; EP 1558627 A1 Based on
 WO 2004037845 A; BR 2003015746 A Based on WO 2004037845 A; JP
 2006507360 W Based on WO 2004037845 A; KR 2005090379 A Based on WO
 2004037845 A

PRAI GB 2003-1505 20030122
 GB 2002-25106 20021028

AB WO 2004037845 A1 UPAB: 20060121
 NOVELTY - Preparation of 3-hydroxy-5beta-H-steroidal sapogenin (I) or its
 derivative comprises reduction of 3-keto-5beta-H-steroidal sapogenin using a
 reducing agent comprising a hindered organoborane or an organo-aluminium
 hydride. ACTIVITY - Nootropic.
 No details of tests for nootropic activity are given.
 MECHANISM OF ACTION - None given in the source material.
 USE - (I) are useful for the treatment of cognitive dysfunction.
 ADVANTAGE - (I) are suitable for use in contact with the tissues of humans and
 lower animals without undue toxicity, irritation, allergic response.

TECH ORGANIC CHEMISTRY - Preferred Process: The reducing agent is a hindered
 organoborane reagent in which organic groups contain more than two
 carbon atoms and the sapogenin obtained is predominantly a
 3beta-hydroxy, 5beta-H-sapogenin. The molar ratio of the
 predominant sapogenin obtained to the alternative 3-epimer, is
 at least 15:1 (preferably 10:1).
 Preferred Components: The hindered organoborane is lithium
 tri-sec-butylborohydride (preferred), potassium tri-sec-butylborohydride,
 sodium tri-sec-butylborohydride, lithium trisiamylborohydride, potassium
 trisiamylborohydride, potassium triphenylborohydride and lithium
 triphenylborohydride. The organo-aluminium hydride is
 lithium tri-tert-butoxyaluminumhydride. Preparation is performed in an
 organic solvent such as tetrahydrofuran, toluene, 1,4-dioxan,
 2-methyltetrahydrofuran (preferred), tert-butyl methyl ether and/or
 diethoxymethane. (I) is sarsasapogenin,
 episarsasapogenin, smilagenin, epismilagenin
 and its esters. The delta4, 3-keto steroidal sapogenin is
 diosgenone (diosgenone is obtained by oxidation of
 diosgenin). The desired sapogenin is formula (A).
 R1, R2, R3, R4, R5, R6, R7, R8 and R9 = H, 1-4C alkyl, OH, or OR (where R
 is 6-12C aryl or 1-4C alkyl); or
 R5+R6 = carbonyl or protected carbonyl group (the stereochemistry at
 carbon centre 3 can be either R or S); and
 R10 = OH, O-linked sugar group or any organic ester group.

ABEX SPECIFIC COMPOUNDS - The use of sarsasapogenin,
 episarsasapogenin, smilagenin, epismilagenin
 is specifically claimed as (I).

EXAMPLE - No suitable example given.

L55 ANSWER 2 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 AN 2003-902924 [82] WPIX Full-text
 CR 2003-229198
 DNC C2003-256428 [82]
 TI Use of steroidal sapogenin derivatives in the preparation of
 compositions for treating e.g. non-cognitive neurodegeneration
 DC B01; D13
 IN GUNNING P; HU Y; ORSI A; REES D; XIA Z
 PA (GUNN-I) GUNNING P; (HUYI-I) HU Y; (ORSI-I) ORSI A; (PHYT-N)
 PHYTOPHARM PLC; (REES-I) REES D; (XIAZ-I) XIA Z

CYC 103

PIA WO 2003082893 A2 20031009 (200382)* EN 30[6]
 AU 2003229877 A1 20031013 (200435) EN
 EP 1490071 A2 20041229 (200502) EN
 BR 2003008788 A 20050111 (200512) PT
 KR 2004093153 A 20041104 (200517) KO
 NO 2004004468 A 20041223 (200520) NO
 US 20050130948 A1 20050616 (200540) EN
 JP 2005528370 W 20050922 (200563) JA 56
 MX 2004009321 A1 20050201 (200564) ES
 TW 2004000042 A 20040101 (200569) ZH
 CN 1642558 A 20050720 (200575) ZH
 NZ 535093 A 20060929 (200668) EN

ADT WO 2003082893 A2 WO 2003-GB1380 20030327; AU 2003229877 A1 AU 2003-229877 20030327; BR 2003008788 A BR 2003-8788 20030327; CN 1642558 A CN 2003-807188 20030327; EP 1490071 A2 EP 2003-722713 20030327; JP 2005528370 W JP 2003-580357 20030327; TW 2004000042 A TW 2003-106926 20030327; EP 1490071 A2 WO 2003-GB1380 20030327; BR 2003008788 A WO 2003-GB1380 20030327; NO 2004004468 A WO 2003-GB1380 20030327; US 20050130948 A1 WO 2003-GB1380 20030327; JP 2005528370 W WO 2003-GB1380 20030327; MX 2004009321 A1 WO 2003-GB1380 20030327; KR 2004093153 A KR 2004-714567 20040916; MX 2004009321 A1 MX 2004-9321 20040924; NO 2004004468 A NO 2004-4468 20041020; US 20050130948 A1 US 2005-507000 20050124; NZ 535093 A NZ 2003-535093 20030327; NZ 535093 A WO 2003-GB1380 20030327

FDT AU 2003229877 A1 Based on WO 2003082893 A; EP 1490071 A2 Based on WO 2003082893 A; BR 2003008788 A Based on WO 2003082893 A; JP 2005528370 W Based on WO 2003082893 A; MX 2004009321 A1 Based on WO 2003082893 A; NZ 535093 A Based on WO 2003082893 A

PRAI US 2002-368178P 20020328
 AR 2002-101170 20020327
 WO 2002-GB1578 20020328

AB WO 2003082893 A2 UPAB: 20060203

NOVELTY - Use of one or more steroidal sapogenin derivatives (I)-(III) in the preparation of compositions for treating non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration, or receptor dysfunction or loss in the absence of cognitive, neural and neuromuscular impairment, is new.

DETAILED DESCRIPTION - Use of one or more steroidal sapogenin derivatives of formula (I)-(III), their stereoisomers, racemic mixtures, pro-drugs and/or salts (containing at least one X substituent; and the carbon atom at the 3-position, or in case of (II) and (III), the 3-position carbon and/or the 26-position carbon carries an O-sugar moiety in which sugar group is mono- to tri-saccharide) in the preparation of compositions for treating non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration, or receptor dysfunction or loss in the absence of cognitive, neural and neuromuscular impairment, is new.

R1-R8, R10, R13, R18-R24, R26-R32, R34, R36, R37, R35a = T or =O; T = H, OH, halo, MeS, MeSO, MeSO₂, N3, NH₂, MeSO₂NH, alkyl, absent or OR;

R = alkyl or acyl;

R9, R11, R12, R15-R17, R25, R35 = T; R14, R33 = T or alkyl;

R33a = T, =O or alkyl;

dotted line = optional double bond; and X = halo, MeS, MeSO, MeSO₂, N3, NH₂, MeSO₂NH- or alkyl; provided that R25 in (III) is in beta-orientation. ACTIVITY - Neuroprotective; CNS-Gen; Muscular-Gen.; Nootropic; Antiparkinsonian; Antidepressant; Neuroleptic; Ophthalmological; Anticonvulsant; Hypertensive; Vulnerary; Cerebroprotective; Tranquillizer; Antiinflammatory; Immunomodulator; Antidiabetic; Vasotropic; Cardiant; Antiasthmatic.

The neuroprotective effect of sarsasapogenin (Ia) was evaluated in aged Sprague-Dawley rats by administration of (Ia) (18 mg/kg/day) through food for 2-3 months. The learning and memory abilities were assessed by using a Y-maze

apparatus and dopamine receptor density was assessed in the brain homogenate by the dual-site competitive ligand binding assay. The dopamine (D1/D2) receptor density was 157/200.6 fmol/mg protein in young rats (control 1); 129.2/153.8 fmol/mg protein in aged rats not receiving (Ia) (control 2); and 172/206.4 fmol/mg protein in aged rats receiving (Ia). In control 1/control 2/(Ia), muscarinic receptor density was 1000/875/1025 fmol/mg protein; and the learning and memory ability was 5.2/2/5.2 (no units), respectively. The results showed that (Ia) restored the dopamine and muscarinic receptors density as well as learning ability and memory in the aged rats by reversing the neuroimpairments.

MECHANISM OF ACTION - None given.

USE - For treating non-cognitive neurodegeneration; non-cognitive neuromuscular degeneration; motor-sensory neurodegeneration; and receptor dysfunction or loss in the absence of cognitive, neural and neuromuscular impairment (e.g. Parkinson's disease, postencephalitic Parkinsonism, depression, schizophrenia, muscular dystrophy (including facioscapulohumeral muscular dystrophy (FSH), Duchenne muscular dystrophy, Becker muscular dystrophy and Bruce's muscular dystrophy, Fuch's dystrophy, myotonic dystrophy, corneal dystrophy, reflex sympathetic dystrophy syndrome (RSDSA), neurovascular dystrophy), myasthenia gravis, Lambert Eaton disease, Huntington's disease, motor neuron diseases (including amyotrophic lateral sclerosis (ALS), multiple sclerosis), postural hypotension, traumatic neurodegeneration e.g. following stroke or following an accident (e.g. traumatic head injury or spinal cord injury), Batten's disease, Cockayne syndrome, Down syndrome, corticobasal ganglionic degeneration, multiple system atrophy, cerebral atrophy, olivopontocerebellar atrophy, dentatorubral atrophy, pallidolusian atrophy, spinobulbar atrophy, optic neuritis, sclerosing pan-encephalitis (SSPE), attention deficit disorder, post-viral encephalitis, post-poliomyelitis syndrome, Fahr's syndrome, Joubert syndrome, Guillain-Barre syndrome, lissencephaly, Moyamoya disease, neuronal migration disorders, autistic syndrome, polyglutamine disease, Niemann-Pick disease, progressive multifocal leukoencephalopathy, pseudotumor cerebri, Refsum disease, Zellweger syndrome, supranuclear palsy, Friedreich's ataxia, spinocerebellar ataxia type 2, Rhetts syndrome, Shy-Drager syndrome, tuberous sclerosis, Pick's disease, chronic fatigue syndrome, neuropathies including hereditary neuropathy, diabetic neuropathy and mitotic neuropathy, prion-based neurodegeneration (including Creutzfeldt-Jakob disease (CJD), variant CJD, new variant CJD, bovine spongiform encephalopathy (BSE), GSS, FFI, kuru and Alper's syndrome), Joseph's disease, acute disseminated encephalomyelitis, arachnoiditis, vascular lesions of the central nervous system, loss of extremity neuronal function, Charcot-Marie-Tooth disease, susceptibility to heart failure, asthma, or macular degeneration) in human and non-human animals (claimed).

ADVANTAGE - The compounds are strongly neuroprotective, stimulative of neurite outgrowth, and preventive of neurotoxicity. The compounds slow or reverse decrease in cholinergic and dopamine receptor density. The compounds reverse the receptor loss effects, simultaneously reversing the deterioration towards the normal or young state with protection. The compounds reverse the apoptotic effect in the non-neoplastic domain of cell life.

TECH

PHARMACEUTICALS - Preferred Components: The steroidal sapogenin derivative is present in a composition selected from pharmaceutical composition, foodstuff, food supplement or beverage; and is present with at least one additional active agent. The additional active agent is cholinesterase inhibitor, dopamine agonist, COMT inhibitor, MAO-B inhibitor, anti-cholinergic, acetylcholine agonist, serotonin agonist, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor agonist, gamma-aminobutyric acid (GABA) receptor agonist, N-methyl-D-aspartate (NMDA) receptor agonist, beta-adrenoceptor agonist, digoxin, dobutamine, anti-inflammatory, neurotrophic factor, statin,

adenosine A2a receptor antagonist, aldose reductase inhibitor, immunomodulator, cannabinoid agonist, interferon beta or tricyclic anti-depressant.

ABEX ADMINISTRATION - Administration of (I)-(III) is more than 0.1 or 0.3 (preferably 1-10) mg/kg/day orally, by sprays, by inhalation, as suppositories or by injection (including liposome preparation).

SPECIFIC COMPOUNDS - Use of 148 compounds (I)-(III) is specifically claimed, e.g. sarsasapogenin (Ia).

EXAMPLE - No relevant example given.

L55 ANSWER 3 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

AN 2003-765551 [72] WPIX Full-text

CR 2001-541229; 1999-496233; 2000-604069; 2001-343159

DNC C2003-210173 [72]

TI Treating and preventing cognitive dysfunction e.g. Alzheimer's disease, Parkinson's disease and autism comprises administering 5-hydroxysapogenin derivative

DC B01; D13

IN BARRACLOUGH P; GUNNING P; HANSON J; HU Y; REES D; XIA Z

PA (BARR-I) BARRACLOUGH P; (GUNN-I) GUNNING P; (HANS-I) HANSON J; (HUYI-I) HU Y; (REES-I) REES D; (XIAZ-I) XIA Z

CYC 1

PIA US 20030100542 A1 20030529 (200372)* EN 14[2]

ADT US 20030100542 A1 CIP of WO 2000-GB3750 20000929; US 20030100542 A1 US 2002-108737 20020328

PRAI US 2002-108737 20020328
WO 2000-GB3750 20000929

AB US 20030100542 A1 UPAB: 20050601

NOVELTY - Treating and preventing cognitive dysfunction comprises administering a 5-hydroxysapogenin derivative (I).

DETAILED DESCRIPTION - Treating and preventing cognitive dysfunction comprises administering a 5-hydroxysapogenin derivative of formula (IA), its stereoisomers, racemic mixtures, prodrugs or salts.

R1-R8, R10 = H, OH, O or OR; R = alkyl, acyl or carbamoyl (all optionally substituted), or alkoxy carbonyl;

R9, R11-R13 = H, OH or OR, and R14 = optionally substituted alkyl. The stereochemistry at 5C is (R) or (S). When (I) is in prodrug form, at least one of the above groups carries a group hydrolyzed off in vivo to form (I).

INDEPENDENT CLAIMS are also included for: (1) a pharmaceutical composition comprises (I), its pro-drug or salt in association with at least one carrier, diluent or excipient, and (2) new compounds (I), provided that when R1, R2, R4, R9 and R10 are H or OH, R6, R7 and R11-R13 are H, R5 and R8 are H, OH or O, R14 is methyl or =CH2 and a is single bond, then R3 is not OH, OCOCH3, OCOC15H31 or O.

ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Hypotensive; Muscular-Gen.; CNS-Gen; Immunomodulator.

MECHANISM OF ACTION - Muscarinic receptor agonist; Nicotinic receptor agonist; Dopamine receptor agonist. In a test for evaluating the effect of anzurogenin D (Ia) on the expression of muscarinic (M2) receptors on Chinese hamster ovary (CHO) cells transfected with DNA for the M2 receptor, results showed that the effect of (Ia) on the expression of M2 receptors was 22%.

USE - Used for treating or preventing age-related cognition, Alzheimer's disease, senile dementia of the Alzheimer's type, Parkinson's disease, Lewy body dementia, postural hypotension, autism, chronic fatigue syndrome, Myasthenia Gravis, Lambert Eaton disease and problems associated with aging, and for treating a condition mediated by the presence of neurofibrillary tangles and beta-amyloid plaques (all claimed).

ADVANTAGE - (I) Selectively increases muscarinic receptor number, which increases synaptic transmission. (I) Increases stimulation of protein kinase C (PKC) with consequential increase in alpha-secretory activity, which reduces

the production of beta-amyloid, plaque formation and neuronal loss. (I) Also increases amyloid precursor proteins-alpha (APPsalpha), which improves cerebral function.

TECH

PHARMACEUTICALS - Preferred Composition: The composition comprises (I) in the form of an extract derived from a plant of Smilax, Asparagus, Anemarrhena, Yucca or Agave.

ORGANIC CHEMISTRY - Preparation: (I) Are prepared by known methods e.g. described by R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

ABEX ADMINISTRATION - Administration is in the form of a foodstuff, food supplement or beverage (claimed). No dosage is given.

EXAMPLE - None given.

L55 ANSWER 4 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

AN 2003-229198 [22] WPIX Full-text

CR 2003-902924

DNC C2003-058766 [22]

TI New use of sapogenin derivatives in the preparation of composition for the treatment or prevention of non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration e.g. Alzheimer's disease

DC B01

IN BARRACLOUGH P; GUNNING P; HANSON J; HU Y; REES D; XIA Z

PA (BARR-I) BARRACLOUGH P; (GUNN-I) GUNNING P; (HANS-I) HANSON J; (HUYI-I) HU Y; (PHYT-N) PHYTOPHARM LTD; (PHYT-N) PHYTOTECH LTD; (REES-I) REES D; (XIAZ-I) XIA Z; (PHYT-N) PHYTOPHARM PLC

CYC 99

PIA WO 2002079221 A2 20021010 (200322)* EN 52[5] <--

NO 2003004364 A 20031128 (200407) NO

EP 1383787 A2 20040128 (200409) EN

BR 2002008533 A 20040420 (200428) PT

AU 2002242894 A1 20021015 (200432) EN <--

CZ 2003002620 A3 20040414 (200435) CS

KR 2004007479 A 20040124 (200435) KO

US 20040147495 A1 20040729 (200450) EN

JP 2004525945 W 20040826 (200456) JA 98

MX 2003008800 A1 20041201 (200561) ES

IN 2003CN01687 P4 20051125 (200604) EN

NZ 529136 A 20051223 (200605) EN

CN 1678325 A 20051005 (200606) ZH

NZ 540712 A 20070126 (200711) EN

ADT WO 2002079221 A2 WO 2002-GB1578 20020328; AU 2002242894 A1

AU 2002-242894 20020328; BR 2002008533 A BR 2002-8533

20020328; CN 1678325 A CN 2002-807427 20020328; EP 1383787

A2 EP 2002-708534 20020328; JP 2004525945 W JP 2002-577845

20020328; NZ 529136 A NZ 2002-529136 20020328; NO

2003004364 A WO 2002-GB1578 20020328; EP 1383787 A2 WO

2002-GB1578 20020328; BR 2002008533 A WO 2002-GB1578 20020328

; CZ 2003002620 A3 WO 2002-GB1578 20020328; US 20040147495 A1

WO 2002-GB1578 20020328; JP 2004525945 W WO 2002-GB1578

20020328; MX 2003008800 A1 WO 2002-GB1578 20020328; IN

2003CN01687 P4 WO 2002-GB1578 20020328; NZ 529136 A WO

2002-GB1578 20020328; CZ 2003002620 A3 CZ 2003-2620 20020328

; MX 2003008800 A1 MX 2003-8800 20030926; KR 2004007479 A KR 2003-712755

20030929; NO 2003004364 A NO 2003-4364 20030929; IN 2003CN01687 P4 IN

2003-CN1687 20031023; US 20040147495 A1 US 2004-472892 20040304; NZ 540712

A Div Ex NZ 2002-280302 20020328; NZ 540712 A NZ

2002-540712 20020328

FDT EP 1383787 A2 Based on WO 2002079221 A; BR 2002008533 A Based on

WO 2002079221 A; AU 2002242894 A1 Based on WO 2002079221 A; CZ
 2003002620 A3 Based on WO 2002079221 A; JP 2004525945 W Based on WO
 2002079221 A; MX 2003008800 A1 Based on WO 2002079221 A; NZ 529136
 A Based on WO 2002079221 A; NZ 540712 A Div ex NZ 529136 A

PRAI GB 2001-7822 20010328

AR 2002-101170 20020327

AB WO 2002079221 A2 UPAB: 20060119

NOVELTY - New use of sapogenin derivatives in the preparation of composition for the treatment or prevention of non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration or receptor loss in the absence of cognitive, neural and neuromuscular impairment in human and non-human animals. DETAILED DESCRIPTION - New use for sapogenin derivatives of formula (II), their stereoisomers, racemic mixtures or their salts, in the preparation of composition for the treatment or prevention of: (1) non-cognitive neurodegeneration; (2) non-cognitive neuromuscular degeneration; or (3) receptor loss in the absence of cognitive, neural and neuromuscular impairment in human and non-human animals suffering from or susceptible to it. R = H, alkoxycarbonyl or alkylcarbonyl (where the alkyl is optionally substituted by aryl, amino, mono- or di-alkyl amino or carboxylic acid residue).

INDEPENDENT CLAIMS are also included for: (1) compounds of formula (II) (where R is alkoxycarbonyl or alkylcarbonyl (where the alkyl is optionally substituted by aryl, amino, alkoxycarbonylamino, mono-alkylamino, di-alkylamino, N-alkyl, N-alkoxycarbonylamino or carboxylic acid residue)) with the provision that:

(a) when the stereochemistry of 3C is alpha and of 25C is S simultaneously, R is not unsubstituted acetyl; (b) when the stereochemistry of 3C is S(beta) and of 25C is R simultaneously, R is not unsubstituted ethoxycarbonyl; (c) when the stereochemistry of 3C is S(beta) and of 25C is S; or the stereochemistry of 3C is R(alpha) or S(beta) and of 25C is R; then R is not succinyl; and (d) when the stereochemistry of 25C is R and the stereochemistry of 3C is S(beta), R is not propionyl, butyryl, valeryl, isovaleryl, (iso)caproyl, diethylacetyl, octanoyl, decanoyl, lauryl, myristyl, palmityl, stearyl, benzoyl, phenylacetyl, phenylpropionate, cinnamate, para-nitrobenzoate, 3,5-dinitrobenzoate, para-chlorobenzoate, 2,4-dichlorobenzoyl, para-bromobenzoyl, meta-bromobenzoyl, para-methoxybenzoyl, furoyl or phthalyl; (2) a method of synthesizing compounds of formula (II) (other than those with R is H); (3) a method of synthesizing a steroidal sapogenin derivative comprising treating a steroidal sapogenin with ethylchloroformate in the presence of a base to form the 3-ethoxycarbonyl derivative; (4) a method of synthesizing a steroidal sapogenin derivative (B) comprising treating a selected steroidal sapogenin with ethylchloroformate or related reagent in the presence of a base; (5) a method of synthesizing episarsasapogenin cathylate from episarsasapogenin comprising treating episarsasapogenin with ethylchloroformate or related reagent and base or succinic anhydride or related reagent and a base; and (6) a composition (A) comprising (II) with the provisions (a) - (d).

ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Hypertensive; Antiasthmatic; Cardiant; Virucide.

MECHANISM OF ACTION - Receptor regulators; Muscarinic receptor stimulator. Sarsasapogenin was tested for brain muscarinic receptor density in Alzheimer's disease model. Three months old, Sprague Dawley rats were divided into two groups. Injection of amyloid betal-40 and ibotenic acid was accomplished. The dose for each rat was amyloid betal-40 (4 microg) and ibotenic acid (1 microg) in saline (1 microl). The injection was completed in 20 minutes and the needle was withdrawn 10 minutes later. One group of rats was given sarsasapogenin cathylate (18 mg/kg/day) (test) as stable suspension in CMC-Na once daily through gastric tube. The other group (control) was given same volume of CMC-Na (i.e. normal saline) once daily. The drugs were administered to the rats for 2 months, starting 20 days before operation. The brain samples were

homogenized, centrifuged and the pellets of the centrifugation were re-homogenized and used for measurement. The effect of test on memory was assessed using step-through test. The experiment was carried out on rats on two consecutive days. On the first day, the rats were adapted in the box for first 3 minutes and then put in light room with its back toward the hole and the copper rods of the dark room were charged for 5 minutes. On second day the rats were tested. The muscarinic receptor density in Alzheimer's model brain in the test/control was (fmol/mg/protein): 916+/-158/859+/-101.

The results showed that the muscarinic receptor density in Alzheimer's model brain in the test was lower than in the control. The test showed significant elevation in brain muscarinic receptor density. The results showed that the test normalized receptor number i.e. they restored receptor number to normal levels.

USE - (II) are used in the manufacture of a composition or medicament for the treatment or prevention of non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration and receptor loss in the absence of cognitive, neural and neuromuscular impairment in human or non-human animals; for treating or preventing cognitive dysfunction e.g. Alzheimer's disease, senile dementia of the Alzheimer's type, SDAT, AAMI, Lewi body dementia and autism in human or non-human animals; in the treatment of disorders such as Parkinson's disease, muscular dystrophy including facioscapulohumeral muscular dystrophy (FSH), Duchenne muscular dystrophy, Becker muscular dystrophy and Bruce's muscular dystrophy, Fuchs' dystrophy, myotonic dystrophy, corneal dystrophy, reflex sympathetic dystrophy syndrome (RSDSA), epilepsy, disease and problems associated with ageing, neurovascular dystrophy, myasthenia gravis, Lambert Eaton disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, postural hypotension, chronic fatigue syndrome, asthma, susceptibility to heart failure, and macular degeneration; in age-related cognitive dysfunction. Also, (II) are used as a foodstuff, food product, food supplement or beverage (claimed); or in the treatment of viral diseases.

ADVANTAGE - (II) increases the receptor number or turnover and enhances the function of receptors in a human or non-human animals. (II) prevents or reverses the loss of muscarinic receptors or dopamine receptors in the brain. (II) reverses the loss of, and/or increases muscarinic receptor number leading to increased synaptic transmission. The reversal of the loss of and/or increase in the number of nicotinic receptors, which lies upstream of the synaptic cleft leads to increase in the reversal of loss of acetylcholine release into the synaptic cleft, thus increasing muscarinic receptor activation and amplifying the overall effect. (II) increases receptor numbers leading to reduced production of beta-amyloid and consequent reduction of plaque formation and neuronal loss. (II) increases amyloid precursor protein (APP)s-alpha and improves cerebral function by improving short and long term memory.

TECH

ORGANIC CHEMISTRY - Preferred Components: (II) has 25C methyl group in R or S configuration.

The compound L-R' is carboxylic acid, an anhydride or an acyl halide.

The base is dry pyridine dissolved in dry dichloromethane.

Preparation: (II) is prepared (other than those with R is H) by reacting (II) (where R is H) with a compound of formula L-R' under nucleophilic substitution conditions.

R' = alkoxycarbonyl or alkylcarbonyl (where the alkyl is optionally substituted by aryl, amino, mono-alkylamino, di-alkylamino, or carboxylic acid residue.

(B) is epismilagenin cathylate (synthesized from epismilagenin), and sarsasapogenin cathylate (synthesized from sarsasapogenin).

BIOLOGY - Preferred Extract: The sarsasapogenin is in the form of a plant extract or dry powdered, plant material, derived from a plant e.g. Smilax Asparagus, Anemarrhena, Dioscorea, Yucca or Agave.

FOOD - Preferred Composition: (A) is a foodstuff, food supplement or beverage.

ABEX DEFINITIONS - Preferred Definitions: - R = lower alkoxy carbonyl or lower alkyl carbonyl optionally substituted by terminal carboxylic acid residue.
 ADMINISTRATION - (II) is administered in a dosage of 1 - 25 (preferably 1 - 10) mg/kg by inhalation, as spray, as liquid or liposome preparation.
 SPECIFIC COMPOUNDS - The use of 40 compounds of formula (II) are specifically claimed, e.g. sarsasapogenin.

L55 ANSWER 5 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

AN 2001-541229 [60] WPIX Full-text

CR 1999-496233; 2000-604069; 2001-343159; 2003-765551

DNC C2001-161463 [60]

TI New sapogenin derivatives, useful for treating e.g. cognitive dysfunction, Parkinson's disease, postural hypotension, autism, chronic fatigue syndrome and ageing problems by increasing muscarinic receptor number and function

DC B01

IN BARRACLOUGH P; GUNNING P; HANSON J; HU Y; REES D; TOBIN A; XIA Z

PA (PHYT-N) PHYTOPHARM PLC

CYC 93

PIA	WO 2001023408	A1	20010405 (200160)*	EN	31[2]	<--
	AU 2000075387	A	20010430 (200160)	EN		<--
	BR 2000014372	A	20020625 (200251)	PT		<--
	EP 1224207	A1	20020724 (200256)	EN		<--
	CN 1377366	A	20021030 (200314)	ZH		
	JP 2003525869	W	20030902 (200358)	JA	36	
	MX 2002003307	A1	20021001 (200370)	ES		<--
	EP 1224207	B1	20060215 (200614)	EN		
	DE 60026046	E	20060420 (200628)	DE		
	US 20060165757	A1	20060727 (200650)	EN		
	ES 2257321	T3	20060801 (200652)	ES		
	DE 60026046	T2	20061005 (200665)	DE		

ADT WO 2001023408 A1 WO 2000-GB3750 20000929; US 20060165757 A1 CIP of WO 1999-GB951 19990326; AU 2000075387 A AU 2000-75387 20000929; BR 2000014372 A BR 2000-14372 20000929; CN 1377366 A CN 2000-813604 20000929; DE 60026046 E DE 2000-626046 20000929; EP 1224207 A1 EP 2000-964452 20000929; EP 1224207 B1 EP 2000-964452 20000929; DE 60026046 E EP 2000-964452 20000929; ES 2257321 T3 EP 2000-964452 20000929; BR 2000014372 A WO 2000-GB3750 20000929; EP 1224207 A1 WO 2000-GB3750 20000929; JP 2003525869 W WO 2000-GB3750 20000929; MX 2002003307 A1 WO 2000-GB3750 20000929; EP 1224207 B1 WO 2000-GB3750 20000929; DE 60026046 E WO 2000-GB3750 20000929; US 20060165757 A1 CIP of WO 2000-GB3750 20000929; JP 2003525869 W JP 2001-526558 20000929; MX 2002003307 A1 MX 2002-3307 20020327; US 20060165757 A1 Cont of US 2002-108737 20020328; US 20060165757 A1 US 2006-346046 20060202; DE 60026046 T2 DE 2000-626046 20000929; DE 60026046 T2 EP 2000-964452 20000929; DE 60026046 T2 WO 2000-GB3750 20000929

FDT DE 60026046 E Based on EP 1224207 A; ES 2257321 T3 Based on EP 1224207 A; AU 2000075387 A Based on WO 2001023408 A; BR 2000014372 A Based on WO 2001023408 A; EP 1224207 A1 Based on WO 2001023408 A; JP 2003525869 W Based on WO 2001023408 A; MX 2002003307 A1 Based on WO 2001023408 A; EP 1224207 B1 Based on WO 2001023408 A; DE 60026046 E Based on WO 2001023408 A; DE 60026046 T2 Based on EP 1224207 A; DE 60026046 T2 Based on WO 2001023408 A

PRAI GE 1999-23078 19990929

AB WO 2001023408 A1 UPAB: 20050526

NOVELTY - Sapogenin derivatives (I) and their stereoisomers and racemic mixtures, pro-drugs and salts are new.

DETAILED DESCRIPTION - Sapogenin derivatives of formula (I) and their stereoisomers and racemic mixtures, pro-drugs and salts are new.

R1 - R8, R10 = H, OH, =O, or OR; R = optionally substituted alkyl, acyl, or carbamoyl, or alkoxycarbonyl;

R9, R11 - R13 = H, OH, or OR; R14 = optionally substituted alkyl; and dashed line = optional double bond; the stereochemistry at C5 can be either R or S.

INDEPENDENT CLAIMS are also included for: (1) the use of (I) in the manufacture of a medicament for increasing the muscarinic receptor number or enhancing the function of muscarinic receptors;

(2) a pharmaceutical composition having cognitive function enhancing properties in the form of an extract derived from a plant of the genus Smilax, Asparagus, Anemarrhena, Yucca, or Agave; (3) a non-therapeutic method of enhancing cognitive function; and (4) the use of (I) in a food product or beverage to enhance cognitive function.

ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Hypertensive.

MECHANISM OF ACTION - Increase muscarinic receptor number and function.

The effect of sapogenin derivatives on muscarinic receptor density in Chinese hamster ovary (CHO) cells expressing recombinant human muscarinic receptors was studied. CHO cells expressing high levels of receptor (approximately 2.2 moles receptor/mg protein) were cultured in flasks (150ml) for 24 hours before the start of the experiment. Vehicle (DMSO) and sapogenin derivative (at 1 and 10microM) were added to the medium for 48 hours. The culture medium was discarded, the cells scraped off and resuspended in Hanks solution, centrifuged and m-receptor levels determined by incubating with (3H)-QNB for 30 minutes followed by liquid scintillation counting. Protein levels were determined by a micro Lowry method. The results showed that over the culturing period treatment with sapogenin derivatives prevents the decrease in muscarinic receptor number in a concentration-dependent manner.

USE - The compounds can be used for increasing the muscarinic receptor number or enhancing the function of muscarinic receptors in a human or non-human animal (claimed). They can be used for treating cognitive dysfunction, Alzheimer's disease, senile dementia of the Alzheimer's type, Parkinson's disease, Lewi body dementia, postural hypotension, autism, chronic fatigue syndrome, myasthenia gravis, Lambert Eaton disease, diseases and problems associated with Gulf War syndrome, occupational exposure to organophosphorus compounds and problems associated with ageing (claimed). They can also be used to enhance cognitive function in a patient suffering from age-related cognitive dysfunction (claimed). They can be used to treat a condition characterized by the presence of neurofibrillary tangles and/or beta-amyloid plaques (claimed).

TECH

ORGANIC CHEMISTRY - Preparation: (I) can be prepared by synthetic methods from unsubstituted sapogenins. The reactions may involve the substitution of one OH-group by the functional radical desired, smilagenin and epismilagenin are preferred as starting products.

ABEX DEFINITIONS - Preferred definitions: - R1, R2, R4, R6, R7, R8, R10, R11, R9, R12, R13 = H; - R3, R5 = OH or OCOCH3, or =O; and - R14 = CH3.

ADMINISTRATION - None given.

SPECIFIC COMPOUNDS - A preferred compound, Anzurogenin D of formula (Ia) is disclosed.

L55 ANSWER 6 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

AN 2001-475962 [51] WPIX Full-text

DNC C2001-142769 [51]

TI New sapogenin derivatives which increase muscarinic receptors in brain, useful for treating e.g. Alzheimer's or Parkinson's disease, dementia, autism, chronic fatigue syndrome, exposure to organophosphorus

compounds and aging problems

DC B01
 IN BARRACLOUGH P; GUNNING P; HANSON J; HU Y; REES D; XIA Z
 PA (PHYT-N) PHYTOPHARM PLC
 CYC 93
 PIA WO 2001049703 A2 20010712 (200151)* EN 44[1] <--
 AU 2001023862 A 20010716 (200169) EN <--
 EP 1246835 A2 20021009 (200267) EN <--
 JP 2003519624 W 20030624 (200341) JA 67
 US 20030158161 A1 20030821 (200356) EN
 MX 2002006720 A1 20021001 (200370) ES <--
 CN 1452630 A 20031029 (200409) ZH
 BR 2001007691 A 20050322 (200522) PT
 CN 1215080 C 20050817 (200647) ZH
 ADT WO 2001049703 A2 WO 2001-GB48 20010108; AU 2001023862 A AU
 2001-23862 20010108; BR 2001007691 A BR 2001-7691 20010108;
 CN 1452630 A CN 2001-803540 20010108; EP 1246835 A2 EP
 2001-900185 20010108; JP 2003519624 W JP 2001-550243 20010108
 ; EP 1246835 A2 WO 2001-GB48 20010108; JP 2003519624 W WO
 2001-GB48 20010108; US 20030158161 A1 CIP of WO 2001-GB48
 20010108; MX 2002006720 A1 WO 2001-GB48 20010108; BR
 2001007691 A WO 2001-GB48 20010108; US 20030158161 A1 US
 2002-189024 20020703; MX 2002006720 A1 MX 2002-6720 20020705
 ; CN 1215080 C CN 2001-803540 20010108
 FDT AU 2001023862 A Based on WO 2001049703 A; EP 1246835 A2 Based on
 WO 2001049703 A; MX 2002006720 A1 Based on WO 2001049703 A; BR
 2001007691 A Based on WO 2001049703 A; JP 2003519624 W Based on WO
 2001049703 A
 PRAI GB 2000-228 20000106
 AB WO 2001049703 A2 UPAB: 20050902
 NOVELTY - Sapogenin derivatives with at least one X group comprising halo, Me-
 S-, Me-SO-, Me-SO₂-, N₃-, NH₂-, MeSO₂NH- or alkyl, are new.
 ACTIVITY - Neuroprotective; nootropic; antiparkinsonian, hypertensive.
 MECHANISM OF ACTION - (I) Increase the number of muscarinic M₂ receptors in
 the brain.
 A test is described, but no results are given.
 USE - Used in the regulation of cellular activity or for the treatment of a
 condition characterized by a deficiency in postsynaptic membrane-bound
 receptor number or function (claimed). (I) regulate receptors and/or increase
 the number of M₂ receptors in the brain. (I) Are used for treating Alzheimer's
 disease or a senile dementia of the Alzheimer's type, Parkinson's disease,
 Lewi body dementia, postural hypotension, autism, chronic fatigue syndrome,
 myasthenia gravis, Lambert Eaton disease, diseases and problems associated
 with Gulf War syndrome, occupational exposure to organophosphorus compounds
 and problems associated with aging.
 (I) Are also be used to treat a condition characterized by the presence of
 neurofibrillary tangles and/or beta-amyloid plaques, or to enhance cognitive
 function e.g. in a patient suffering from age-related dysfunction.
 TECH ORGANIC CHEMISTRY - Preferred compounds: The sapogenin compounds
 are of formula (I), their stereoisomers, racemic mixtures, prodrugs or
 salts.
 R₁-R₈, R₁₀, R₁₃, R₂₁-R₂₄, R₂₆-R₃₂, R₃₄, R₃₅ = H, OH, =O or OR;
 R = alkyl, acyl or absent;
 R₉, R₁₁, R₁₂, R₁₅-R₁₇, R₂₅ = H, OH or OR;
 R₃₃, R₁₄ = H, alkyl, OH, =O or R, and
 at least one of R₁-R₁₈, R₂₁-R₃₅ = X.
 Preparation: (I) Are prepared from starting materials comprising
 unsubstituted sapogenins obtained from Smilax, Asparagus,
 Anemarrhena, Yucca or Agave.

ABEX ADMINISTRATION - (I) Are used in food products or beverages.
 SPECIFIC COMPOUNDS - 6 Compounds (I) are specifically claimed e.g: -
 3beta-fluoro-5beta, 20alpha,22alpha,25R-spirostane (Ia).
 EXAMPLE - Methylsulfonyl chloride (1.83 g) was added to a solution of
 smilagenin (5.0 g) in dry pyridine (40 ml). The mixture was heated
 on a steam bath for 10 minutes, allowed to stand overnight at room
 temperature and then poured onto ice-water (80 ml). Trituration gave an
 off-white solid, which was removed by filtration and washed with water.
 This material was dried in a vacuum desiccator over CaCl₂ to give 5.70 g
 of crude product. - A sample (1.0 g) was recrystallized from acetone (2 x)
 to give 340 mg of 3beta-methylsulfonyloxy-5beta,20alpha,22alpha,25R-
 spirostane (Ib).

L55 ANSWER 7 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 AN 2001-397532 [42] WPIX Full-text
 DNC C2001-120809 [42]
 TI New sapogenin derivatives, useful for treating e.g. cognitive
 dysfunction, Alzheimer's disease, postural hypotension, autism, chronic
 fatigue syndrome and ageing problems by increasing muscarinic receptor
 number and function
 DC B01
 IN BARRACLOUGH P; GUNNING P; HANSON J; HU Y; REES D; TOBIN A; XIA Z
 PA (BARR-I) BARRACLOUGH P; (GUNN-I) GUNNING P; (HANS-I) HANSON J;
 (HUYI-I) HU Y; (PHYT-N) PHYTOPHARM PLC; (REES-I) REES D;
 (XIAZ-I) XIA Z
 CYC 91
 PIA WO 2001023407 A1 20010405 (200142)* EN 32[2] <--
 AU 2000075382 A 20010430 (200142) EN <--
 BR 2000014355 A 20020716 (200255) PT <--
 EP 1224206 A1 20020724 (200256) EN <--
 US 20020183294 A1 20021205 (200301) EN
 CN 1377367 A 20021030 (200314) ZH
 JP 2003510333 W 20030318 (200321) JA 48
 MX 2002003306 A1 20021001 (200370) ES <--
 EP 1224206 B1 20040922 (200462) EN
 DE 60014136 E 20041028 (200471) DE
 ES 2228608 T3 20050416 (200528) ES
 EP 1548025 A2 20050629 (200543) EN
 DE 60014136 T2 20051006 (200566) DE
 ADT WO 2001023407 A1 WO 2000-GB3745 20000929; AU 2000075382 A
 AU 2000-75382 20000929; BR 2000014355 A BR 2000-14355
 20000929; CN 1377367 A CN 2000-813605 20000929; DE 60014136
 E DE 2000-60014136 20000929; DE 60014136 T2 DE
 2000-60014136 20000929; EP 1224206 A1 EP 2000-964447 20000929
 ; EP 1224206 B1 EP 2000-964447 20000929; DE 60014136 E EP
 2000-964447 20000929; ES 2228608 T3 EP 2000-964447 20000929
 ; EP 1548025 A2 Div Ex EP 2000-964447 20000929; DE 60014136 T2
 EP 2000-964447 20000929; BR 2000014355 A WO 2000-GB3745
 20000929; EP 1224206 A1 WO 2000-GB3745 20000929; US
 20020183294 A1 CIP of WO 2000-GB3745 20000929; JP 2003510333 W
 WO 2000-GB3745 20000929; MX 2002003306 A1 WO 2000-GB3745
 20000929; EP 1224206 B1 WO 2000-GB3745 20000929; DE
 60014136 E WO 2000-GB3745 20000929; DE 60014136 T2 WO
 2000-GB3745 20000929; JP 2003510333 W JP 2001-526557 20000929
 ; MX 2002003306 A1 MX 2002-3306 20020327; US 20020183294 A1
 US 2002-109204 20020328; EP 1548025 A2 EP 2004-21601
 20000929
 FDT DE 60014136 E Based on EP 1224206 A; ES 2228608 T3 Based on EP 1224206 A;
 EP 1548025 A2 Div ex EP 1224206 A; DE 60014136 T2 Based on EP 1224206 A;
 AU 2000075382 A Based on WO 2001023407 A; BR 2000014355 A Based on WO

2001023407 A; EP 1224206 A1 Based on WO 2001023407 A; JP 2003510333 W
Based on WO 2001023407 A; MX 2002003306 A1 Based on WO 2001023407 A; EP
1224206 B1 Based on WO 2001023407 A; DE 60014136 E Based on WO 2001023407
A; DE 60014136 T2 Based on WO 2001023407 A

PRAI GB 1999-23077 19990929

AB WO 2001023407 A1 UPAB: 20060117

NOVELTY - Sapogenin derivatives (I) and (II) and their stereoisomers and racemic mixtures, pro-drugs and salts are new.

DETAILED DESCRIPTION - Sapogenin derivatives of formula (I) and (II) and their stereoisomers and racemic mixtures, pro-drugs and salts are new.

R1 - R8, R10, R17 = H, OH, =O, or OR; R = optionally substituted alkyl, acyl, or carbamoyl, or alkoxy carbonyl;

R9, R11 - R13 = H, OH, or OR; R14 = optionally substituted alkyl; R15, R16 = H, or optionally substituted alkyl or acyl; dashed line = optional double bond; the H at C5 may be either alpha or beta. INDEPENDENT CLAIMS are also included for: (1) the use (I) or (II) for the manufacture of a medicament for increasing the muscarinic receptor number or enhancing the function of muscarinic receptor;

(2) a pharmaceutical composition with cognitive function enhancing properties in the form of an extract derived from a plant of the genus Smilax, Asparagus, Anemarrhena, Yucca or Agave; (3) a non-therapeutic method of enhancing cognitive function; and (4) the use of (I) or (II) in a food product or beverage to enhance cognitive function.

ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Hypertensive.

MECHANISM OF ACTION - Increase muscarinic receptor number and function.

The effect of sapogenin derivatives on muscarinic receptor density in Chinese hamster ovary (CHO) cells expressing recombinant human muscarinic receptors was studied. CHO cells expressing high levels of receptor (approximately 2.2 moles receptor/mg protein) were cultured in flasks (150ml) for 24 hours before the start of the experiment. Vehicle (DMSO) and sapogenin derivative (at 1 and 10microM) were added to the medium for 48 hours. The culture medium was discarded, the cells scraped off and resuspended in Hanks solution, centrifuged and m-receptor levels determined by incubating with (3H)-QNB for 30 minutes followed by liquid scintillation counting. Protein levels were determined by a micro Lowry method. The results showed that over the culturing period treatment with sapogenin derivatives prevents the decrease in muscarinic receptor number in a concentration-dependent manner.

USE - The compounds can be used for increasing the muscarinic receptor number or enhancing the function of muscarinic receptors in a human or non-human animal (claimed). They can be used for treating cognitive dysfunction, Alzheimer's disease, senile dementia of the Alzheimer's type, Parkinson's disease, Lewi body dementia, postural hypotension, autism, chronic fatigue syndrome, myasthenia gravis, Lambert Eaton disease, diseases and problems associated with Gulf War syndrome, occupational exposure to organophosphorus compounds and problems associated with ageing (claimed). They can also be used to enhance cognitive function in a patient suffering from age-related cognitive dysfunction (claimed). They can be used to treat a condition characterized by the presence of neurofibrillary tangles and/or beta-amyloid plaques (claimed).

TECH

ORGANIC CHEMISTRY - (I) and (II) can be prepared by synthetic methods from unsubstituted sapogenins. The reactions may involve the substitution of one OH-group by the functional radical desired, smilagenin and epismilagenin are preferred as starting products.

ABEX ADMINISTRATION - None given

SPECIFIC COMPOUNDS - A preferred compound, E/F-Seco-tigogenin of formula (Ia) is disclosed.

AN 2001-343159 [36] WPIX Full-text
 CR 1999-496233; 2000-604069; 2001-541229; 2003-765551
 DNC C2001-106195 [36]
 TI New sapogenin derivatives, useful for treating e.g. cognitive dysfunction, Alzheimer's disease, Parkinson's disease, autism, chronic fatigue syndrome, and ageing problems by increasing muscarinic receptor number and function
 DC B01; B04
 IN BARRACLOUGH P; GUNNING P; HANSON J; HU Y; REES D; TOBIN A; XIA Z
 PA (BARR-I) BARRACLOUGH P; (GUNN-I) GUNNING P; (HANS-I) HANSON J; (HUYI-I) HU Y; (PHYT-N) PHYTOPHARM PLC; (REES-I) REES D; (XIAZ-I) XIA Z
 CYC 93
 PIA WO 2001023406 A1 20010405 (200136)* EN 43[4] <--
 AU 2000075375 A 20010430 (200142) EN <--
 NO 2002001541 A 20020528 (200248) NO <--
 BR 2000014381 A 20020625 (200251) PT <--
 EP 1224205 A1 20020724 (200256) EN <--
 US 20030004147 A1 20030102 (200305) EN
 CZ 2002001114 A3 20021211 (200309) CS
 CN 1377368 A 20021030 (200314) ZH
 JP 2003510332 W 20030318 (200321) JA 50
 KR 2002092914 A 20021212 (200328) KO
 ZA 2002002382 A 20030923 (200368) EN 61
 MX 2002003305 A1 20021001 (200370) ES <--
 NZ 518596 A 20040730 (200454) EN
 AU 778294 B2 20041125 (200506) EN
 IN 2002CN00430 P4 20050304 (200547) EN
 US 20060100184 A9 20060511 (200633) EN
 EP 1224205 B1 20060510 (200634) EN
 DE 60027913 E 20060614 (200642) DE
 ES 2260055 T3 20061101 (200673) ES
 EP 1724279 A2 20061122 (200677) EN
 US 7138427 B2 20061121 (200677) EN
 US 20060276415 A1 20061207 (200681) EN
 DE 60027913 T2 20070111 (200707) DE
 ADT WO 2001023406 A1 WO 2000-GB3737 20000929; US 20060100184 A9 CIP of WO 1999-GB951 19990326; US 7138427 B2 CIP of WO 1999-GB951 19990326; US 20060276415 A1 CIP of WO 1999-GB951 19990326; IN 2002CN00430 P4 WO 2000-GB3737; AU 2000075375 A AU 2000-75375 20000929; AU 778294 B2 AU 2000-75375 20000929; BR 2000014381 A BR 2000-14381 20000929; CN 1377368 A CN 2000-813606 20000929; DE 60027913 E DE 2000-627913 20000929; EP 1224205 A1 EP 2000-964439 20000929; EP 1224205 B1 EP 2000-964439 20000929; DE 60027913 E EP 2000-964439 20000929; ES 2260055 T3 EP 2000-964439 20000929; EP 1724279 A2 Div Ex EP 2000-964439 20000929; NZ 518596 A NZ 2000-518596 20000929; NO 2002001541 A WO 2000-GB3737 20000929; BR 2000014381 A WO 2000-GB3737 20000929; EP 1224205 A1 WO 2000-GB3737 20000929; US 20030004147 A1 CIP of WO 2000-GB3736 20000929; CZ 2002001114 A3 WO 2000-GB3737 20000929; JP 2003510332 W WO 2000-GB3737 20000929; MX 2002003305 A1 WO 2000-GB3737 20000929; NZ 518596 A WO 2000-GB3737 20000929; US 20060100184 A9 CIP of WO 2000-GB3737 20000929; EP 1224205 B1 WO 2000-GB3737 20000929; DE 60027913 E WO 2000-GB3737 20000929; US 7138427 B2 CIP of WO 2000-GB3737 20000929; US 20060276415 A1 CIP of WO 2000-GB3737 20000929; JP 2003510332 W JP 2001-526556 20000929; US 20060100184 A9 CIP of US 2001-647110 20010111; US 7138427 B2 CIP of US 2001-647110 20010111; CZ 2002001114 A3 CZ 2002-1114 20000929; IN

2002CN00430 P4 IN 2002-CN430 20020321; ZA 2002002382 A ZA
 2002-2382 20020325; KR 2002092914 A KR 2002-703973 20020327
 ; MX 2002003305 A1 MX 2002-3305 20020327; NO 2002001541 A
 NO 2002-1541 20020327; US 20030004147 A1 US 2002-109095
 20020328; US 20060100184 A9 US 2002-109095 20020328; US
 7138427 B2 US 2002-109095 20020328; US 20060276415 A1 Div Ex
 US 2002-109095 20020328; EP 1724279 A2 EP 2006-5887
 20000929; US 20060276415 A1 US 2006-502784 20060811; DE 60027913 T2
 DE 2000-627913 20000929; DE 60027913 T2 EP 2000-964439
 20000929; DE 60027913 T2 WO 2000-GB3737 20000929

FDT AU 778294 B2 Previous Publ AU 2000075375 A; DE 60027913 E
 Based on EP 1224205 A; ES 2260055 T3 Based on EP 1224205 A;
 EP 1724279 A2 Div ex EP 1224205 A; NZ 518596 A Div in NZ
 532211 A; AU 2000075375 A Based on WO 2001023406 A; BR
 2000014381 A Based on WO 2001023406 A; EP 1224205 A1 Based on WO
 2001023406 A; CZ 2002001114 A3 Based on WO 2001023406 A; JP
 2003510332 W Based on WO 2001023406 A; MX 2002003305 A1 Based on WO
 2001023406 A; NZ 518596 A Based on WO 2001023406 A; AU 778294
 B2 Based on WO 2001023406 A; EP 1224205 B1 Based on WO 2001023406
 A; DE 60027913 E Based on WO 2001023406 A; DE 60027913 T2 Based
 on EP 1224205 A; DE 60027913 T2 Based on WO 2001023406 A

PRAI GB 1999-23076 19990929
 GB 1998-6513 19980326
 GB 1999-5275 19990308

AB WO 2001023406 A1 UPAB: 20060117
 NOVELTY - Sapogenin derivatives (I) and (II) and their stereoisomers and
 racemic mixtures, pro-drugs and salts are new.
 DETAILED DESCRIPTION - Sapogenin derivatives of formula (I) and (II) and their
 stereoisomers and racemic mixtures, pro-drugs and salts are new.
 R1 - R8, R10, = H, OH, =O, or OR; R = optionally substituted alkyl or acyl,
 carbamoyl or alkoxycarbonyl;
 R9, R11 - R13 = H, OH, OR;
 R14 = optionally substituted alkyl; R15, = H, optionally substituted alkyl,
 optionally substituted acyl or glucosyl;
 dashed bond = optional double bond, but excluding in (I) where simultaneously
 R1 = R2 = R4 = R5 = R6 = R7 = R8 = R9 = R10 = R11 = R12 = R13 = H;
 R3 = betaOH;
 R14 = CH3;
 the methyl group at C22 is alpha, the C20 is alpha, and there is a S
 configuration at C25.
 INDEPENDENT CLAIMS are also included for: (1) use of (I) and (II) in the
 manufacture of a medicament for increasing the muscarinic receptor number or
 enhancing the function of muscarinic receptors;
 (2) a pharmaceutical composition having cognitive function enhancing
 properties which comprises (I) or (II) in the form of an extract derived from
 a plant of the genus Smilax, Asparagus, Anemarrhena, Yucca or Agave;
 (3) a non-therapeutic method of enhancing cognitive function; and (4) the use
 of (I) or (II) in a food product or beverage to enhance cognitive function.
 ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Hypertensive.
 MECHANISM OF ACTION - Increase muscarinic receptor number and function.
 The effect of sapogenin derivatives on muscarinic receptor density in Chinese
 hamster ovary (CHO) cells expressing recombinant human muscarinic receptors
 was studied. CHO cells expressing high levels of receptor (approximately 2.2
 moles receptor/mg protein) were cultured in flasks (150ml) for 24 hours before
 the start of the experiment. Vehicle (dimethylsulfoxide (DMSO)) and sapogenin
 derivative (at 1 and 10microM) were added to the medium for 48 hours. The
 culture medium was discarded, the cells scraped off and resuspended in Hanks
 solution, centrifuged and m-receptor levels determined by incubating with
 (3H)-QNB for 30 minutes followed by liquid scintillation counting. Protein
 levels were determined by a micro Lowry method. The results showed that over

the culturing period treatment with sapogenin derivatives prevents the decrease in muscarinic receptor number in a concentration-dependent manner. USE - The compounds can be used for increasing the muscarinic receptor number or enhancing the function of muscarinic receptors in a human or non-human animal (claimed). They can be used for treating cognitive dysfunction, Alzheimer's disease, senile dementia of the Alzheimer's type, Parkinson's disease, Lewi body dementia, postural hypotension, autism, chronic fatigue syndrome, myasthenia gravis, Lambert Eaton disease, diseases and problems associated with Gulf War syndrome, occupational exposure to organophosphorus compounds and problems associated with ageing (claimed). They can also be used to enhance cognitive function in a patient suffering from age-related cognitive dysfunction (claimed). They can be used to treat a condition characterized by the presence of neurofibrillary tangles and/or beta-amyloid plaques (claimed).

TECH

ORGANIC CHEMISTRY - (I) and (II) can be prepared by synthetic methods from unsubstituted sapogenins. The reactions may involve the substitution of one OH-group by the functional radical desired, smilagenin and epismilagenin are preferred as starting products.

ABEX ADMINISTRATION - None given.

SPECIFIC COMPOUNDS - Two compounds are specifically claimed, i.e. 3-O-ethoxycarbonyl-5beta, 20alpha, 22alpha, 25R-spirostand-3beta-ol (3-beta-(ethoxycarbonyloxy)-5-alpha-androstano(16,17-b)-(4'-methyl-(5',2''-spiro)-(5''-methylpyrano)furan)) of formula (Ia) and epismilagenin succinate (3-alpha-(carboxyethylcarbonyloxy)-5-alpha-androstano(16,17-b)-(4'-methyl-(5',2''-spiro)-(5''-methylpyrano)furan)) of formula (Ib).

EXAMPLE - Ethyl chloroformate (1.40g) was added dropwise to a stirred solution of smilagenin (2.08g) in anhydrous dichloromethane (15ml) and anhydrous pyridine (1.02g). The mixture was stirred at room temperature for 18 hours and then partitioned between water (30ml) and dichloromethane. The aqueous layer was extracted twice with dichloromethane, the combined organic layers washed with water and then dried over MgSO₄ (anhydrous). The solvent was evaporated in vacuo to give an oil (2.1g) that rapidly crystallized. This material was chromatographed on silica (ca. 70g). Elution with ethyl acetate-hexane (1:9) and recrystallization from methanol afforded white crystals of 3-O-ethoxycarbonyl-5beta, 20alpha, 22alpha, 25R-spirostand-3beta-ol (1.08g), m. pt. 154-156degreesC.

L55 ANSWER 9 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 AN 2000-604069 [58] WPIX Full-text
 CR 1999-496233; 2001-343159; 2001-541229; 2003-765551
 DNC C2000-180835 [58]
 DNN N2000-447105 [58]
 TI Screening compound to assess effectiveness to treat receptor abnormalities in Alzheimer's disease by growing transfected cells beyond usual level to reach equilibrium, removing growth medium, adding test agent
 DC B04; S03
 IN HU Y; REES D; TOBIN A; XIA Z
 PA (PHYT-N) PHYTOPHARM PLC
 CYC 1
 PIA GB 2347676 A 20000913 (200058)* EN 10[2] <--
 ADT GB 2347676 A GB 1999-23075 19990929
 PRAI US 1999-362328 19990728
 GB 1999-5275 19990308
 AB GB 2347676 A UPAB: 20050411
 NOVELTY - Screening a compound (D) to determine its effectiveness to treat condition due to specific receptor (R) depletion, involves dividing cells transfected with (R) into control and test samples (CS; TS) which are grown in

nutrient medium (NM) to reach equilibrium state, removing (NM), adding test (D) dissolved in carrier to (TS) and carrier alone to CS, incubating (R) and determining number of (R).

DETAILED DESCRIPTION - Screening a compound (D) to determine its effectiveness to treat a condition due to specific receptor (R) depletion comprises:

(a) preparing or retrieving suitable cells (C) (e.g. Chinese Hamster Ovary cells) transfected with DNA for the specific receptor or receptor type;
(b) dividing the transfected (C) into two equal portions, one portion to serve as a control sample (CS) and the other to serve as a test sample (TS);
(c) allowing the CS and the TS to grow in the presence of a nutrient medium (NM) until the (C) in the sample approach or reach a state of equilibrium;
(d) removing the NM from both of the sample and then simultaneously adding to the TS the test (D) dissolved in a cytologically acceptable carrier and adding to the CS an equivalent concentration of the carrier; (e) incubating the (C) for a selected time and performing an assay to determine the numbers of (R) present in the (C) of the CS and the TS.

USE - (I) is useful for assessing the effectiveness of compounds for the treatment of conditions caused by deficiency in number or function of membrane bound receptors and also for assessing compounds for treatment of cognitive dysfunction conditions, including Alzheimer's disease and senile dementia.

TECH

BIOTECHNOLOGY - Preferred Method: In (I) the transfected (C) are allowed to reach at least 80% confluence in the step of growing the sample in NM. The incubation period is at least 72 hours.

ABEX EXAMPLE - Chinese Hamster Ovary (CHO) cells transfected with DNA for the human m2 muscarinic receptor expressed high levels of m2 receptors. Frozen cells were removed and plated out onto dishes or flasks and a conventional growth medium containing cell nutrients including fetal calf serum and/or other appropriate nutrient factors) was added. To the test samples a medium containing the test compound dissolved in a cytologically acceptable carrier medium was added and for the control samples, an identical medium except that it contained none of the test compound was added and the medium was removed. Cells were plated on well plates 24 hours before the experiment and were allowed to grow till they reached at least 80% confluence. The medium was then removed and replaced with medium containing vehicle only Dimethyl sulfoxide (DMSO) or medium containing the same vehicle carrying a test compound e.g. sarsasapogenin (10mM). The cells were then incubated. It was found that the number of m2 receptor increased when compared to the control on prolong incubation with sarsasapogenin.

L55 ANSWER 10 OF 10 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 1999-496233 [42] WPIX Full-text
CR 2000-604069; 2001-343159; 2001-541229; 2003-765551
DNC C1999-145657 [42]
TI Composition having cognitive function enhancing properties used to treat e.g. Alzheimer's disease
DC B04
IN BROSTOFF J; GUNNING P; HU Y; MAXTED S K; RUBIN I; RUBIN L; WANG W; WHITTLE B; WHITTLE B A; WNAG W; XIA Z; YAER H; ZONGQIN X; BROSTOFFJONATHAN; GUNNINGPHIL; HUYAER; RUBINIAN; WANGWEIJUN; WHITTLEBRIAN; XIAZONGQIN
PA (BROS-I) BROSTOFF J; (GUNN-I) GUNNING P; (HUYI-I) HU Y; (PHYT-N) PHYTOPHARM P/C; (PHYT-N) PHYTOPHARM PLC; (RUBI-I) RUBIN I; (WANG-I) WANG W; (WHIT-I) WHITTLE B; (XIAZ-I) XIA Z; (NATU-N) NATURAL INPUT SOLUTIONS INC
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US 1998-113352P 19981221

AB GB 2335599 A UPAB: 20060115

NOVELTY - Composition having cognitive function enhancing properties comprises a saponin or sapogenin.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (A) the use of an extract of a plant of the genus Smilax, Asparagus, Anemarrhena, Yucca, or Agave in a medicament having cognitive function enhancing properties; and (B) treatment of a condition characterized by a deficiency in membrane-bound receptor number or function in a tissue, organ, cell type or organelle, comprising, modulating the action of a cytosolic, nuclear or membrane-bound protein or receptor which, when activated by an agonist binding to it, or when its activity is promoted by deactivation of an antagonist, upregulates and/or normalizes the number and/or turnover of membrane-bound receptors in that tissue, organ, cell type or organelle. ACTIVITY - Nootropic; neuroleptic; antiparkinsonian.

MECHANISM OF ACTION - The compositions give increased levels of membrane-bound receptor mRNA, specifically m1 receptor mRNA. 20 Month old pure-line male SD rats were divided randomly into 2 groups. One group received 3 mg of sarsasapogenin per rat per day mixed into the daily feed. The control group received normal food and water. 4 Months later, their brains were used in hybridization technique experiments with 4-6 months old rats used as a young control group. Other feeding arrangements for each group were completely identical. The rats were decapitated and their brains removed intact. Coronal slices (15 micro m thick) were prepared. Studies showed that there was a significant reduction on mRNA expression for m1 receptors in the striatum of aged rats compared to young controls. Administration of sarsasapogenin resulted in a significant increase in m1 receptor mRNA in the same brain area when treated animals were compared to aged, untreated controls.

USE - The composition is used to enhance cognitive function, preferably for the treatment of conditions characterized by a deficiency in postsynaptic membrane-bound receptor number or function, especially Alzheimer's disease or senile dementia of the Alzheimer's type (all claimed).

Other conditions which can be treated include Parkinson's disease, Lewi body dementia, postural hypotension, autism, chronic fatigue syndrome, Myasthenia Gravis, Lambert Eaton disease, diseases and problems associated with Gulf War Syndrome, occupation exposure to organophosphorus, and problems associated with ageing.

ADVANTAGE - The substances used do not have high overt estrogenic, androgenic and/or anabolic activity in patients.

TECH

PHARMACEUTICALS - Preferred Composition: The saponin or sapogenin is a steroidal saponin or sapogenin, preferably non-estrogenic. The saponin or sapogenin is derived from a plant of the genus Smilax, Asparagus, Anemarrhena, Yucca, or Agave. The composition contains: at least two of sarsasapogenin, smilagenin, prazerenin, an astragaloside, tigogenin, hecogenin, and diosgenin; one or more of smilagenin, prazerenin, an astragaloside, tigogenin, hecogenin, and diosgenin; or smilagenin, ananzuogenin D or an astragaloside.

BIOTECHNOLOGY - Preferred Treatment: In (B) the protein or receptor, when activated, increases the amount of mRNA molecules in the tissue, organ, cell type, or organelle which code for membrane bound receptors. This works by increasing the production, transcription or expression, or decreasing the breakdown of the mRNA molecules.

The protein or receptor, when activated modulates the expression of the DNA in the tissue, organ, cell type, or organelle which code for membrane bound receptors.

The protein or receptor, when activated upregulates and/or normalizes the number and/or turnover of muscarinic and/or adrenergic receptors in that tissue, organ, cell type, or organelle.

The action of the receptor is modulated by administration of a substance which is at least a partial agonist of nicotinic receptors. The agonist is preferably saponin or sapogenin, especially sarsasapogenin, smilagenin, prazerenin, an astragaloside, tigogenin, hecogenin, or diosgenin.

The receptor is located in the cytosol of the cells of the tissue, organ, cell type, or organelle. The receptor is a steroid receptor, preferably an estrogen receptor.

=> => d his

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      E PHYTOPHARM/PA
L5      21 S E3-E7
      E PHYTOTECH/PA
L6      19 S E3-E5
      E PHYT/PACO
      E E7+ALL
L7      50 S L1-L6
L8      16 S L7 AND C07J/IPC, IC, ICM, ICS
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      E BACK E1
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L22      2 S E8,E9
L23     2373 S L19-L22
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L26     323 S 06673/RIN
L27     284 S L25 AND L26
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L34      1 S L32 AND (B405(S)Q509)/M0,M1,M2,M3,M4,M5,M6
L35      1 S L32 AND (B505(S)Q509)/M0,M1,M2,M3,M4,M5,M6
L36      1 S L32 AND (A313(S)Q509)/M0,M1,M2,M3,M4,M5,M6
L37      1 S L32 AND Q509/M0,M1,M2,M3,M4,M5,M6
L38      1 S L32 AND (RA34QM OR RA009I OR RA7BP2 OR RA34QR OR RAE8H6 OR RA
L39      4 S L32 AND (ORGANOBORAN? OR ORGANOALUMIN? OR ORGANO () (BORAN? O
L40      3 S L39 NOT L34-L38
L41      1 S L34-L39 NOT L40
L42      31 S L32 AND N412/M0,M1,M2,M3,M4,M5,M6
L43      16 S L42 AND (N243(S)N412)/M0,M1,M2,M3,M4,M5,M6
L44      13 S L42 AND (N243(S)N412(S)N362)/M0,M1,M2,M3,M4,M5,M6
L45      7 S L44 NOT VITAMIN D#
L46      6 S L45 NOT L41
L47      9 S L43 NOT L45
L48      2 S L47 NOT VITAMIN D#
L49      15 S L42 NOT L43-L48
L50      11 S L49 NOT VITAMIN D#
L51      12 S L7 AND L23
L52      17 S L8,L51
L53      10 S L52 AND L32,L33
L54      10 S L41,L53
L55      10 S L54 AND L1-L54
L56      7 S L52 NOT L55

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